Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

Initial diagnostic workup of acute leukemia: guideline from the College of American Pathologists and the American Society of Hematology.

Bibliographic Source(s)

Arber DA, Borowitz MJ, Cessna M, Etzell J, Foucar K, Hasserjian RP, Rizzo JD, Theil K, Wang SA, Smith AT, Rumble RB, Thomas NE, Vardiman JW. Initial diagnostic workup of acute leukemia: guideline from the College of American Pathologists and the American Society of Hematology. Arch Pathol Lab Med. 2017 Oct;141(10):1342-93. [431 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

NEATS Assessment

National Guideline Clearinghouse (NGC) has assessed this guideline's adherence to standards of trustworthiness, derived from the Institute of Medicine's report Clinical Practice Guidelines We Can Trust.

= Poor = Fair = Good = Very Good = Excellent

Assessment	Standard of Trustworthiness
YES	Disclosure of Guideline Funding Source
	Disclosure and Management of Financial Conflict of Interests
	Guideline Development Group Composition
YES	Multidisciplinary Group

YES	Methodologist Involvement
▮▮▮▮▮	Patient and Public Perspectives
	Use of a Systematic Review of Evidence
▮▮▮▮▮	Search Strategy
▮▮▮▮▮	Study Selection
▮▮▮▮▯	Synthesis of Evidence
	Evidence Foundations for and Rating Strength of Recommendations
▮▮▮▮▮	Grading the Quality or Strength of Evidence
▮▮▮▮▮	Benefits and Harms of Recommendations
▮▮▮▮▮	Evidence Summary Supporting Recommendations
▮▮▮▮▮	Rating the Strength of Recommendations
▮▮▮▮▮	**Specific and Unambiguous Articulation of Recommendations**
▮▮▮▮▮	**External Review**
▮▮▮▮▯	**Updating**

Recommendations

Major Recommendations

The grades for the strength of evidence (Convincing, Adequate, Inadequate, Insufficient) for strength of recommendations (Strong recommendation, Recommendation, Expert consensus opinion, No recommendation) are defined at the end of the "Major Recommendations" field.

Guideline Statements

The treating clinician should provide relevant clinical data or ensure that this is readily accessible by the pathologist (Strong recommendation).
Note: These data include, but are not limited to, the patient's age, sex, and ethnicity; history of any hematologic disorder or known predisposing conditions or syndromes; any prior malignancy; exposure to cytotoxic therapy, immunotherapy, radiotherapy, or other possibly toxic substances; and any additional clinical findings of diagnostic or prognostic importance. The treating clinician should also include any history of possibly confounding factors, such as recent growth factor therapy, transfusions or other medications that might obscure or mimic the features of acute leukemia. The treating clinician should also obtain and provide information regarding any family history of any hematologic disorders or other malignancies.
The treating clinician should provide relevant physical examination and imaging findings or ensure that those results are readily accessible by the pathologist (Recommendation).
Note: This includes, but is not limited to, neurologic exam findings and the presence of tumor

masses (e.g., mediastinal), other tissue lesions (e.g., cutaneous), and/or organomegaly.
The pathologist should review recent or concurrent complete blood cell (CBC) counts and leukocyte differentials and evaluate a peripheral blood smear (Strong recommendation).
The treating clinician or pathologist should obtain a fresh bone marrow aspirate for all patients suspected of acute leukemia, a portion of which should be used to make bone marrow aspirate smears for morphologic evaluation. If performed, the pathologist should evaluate an adequate bone marrow trephine core biopsy, bone marrow trephine touch preparations, and/or marrow clots, in conjunction with the bone marrow aspirates (Strong recommendation).
Note: If bone marrow aspirate material is inadequate or if there is compelling clinical reason to avoid bone marrow examination, peripheral blood may be used for diagnosis and ancillary studies if sufficient numbers of blasts are present. If a bone marrow aspirate is unobtainable, touch imprint preparations of a core biopsy should be prepared and evaluated, and an additional core biopsy may be submitted unfixed in tissue culture medium for disaggregation for flow and genetic studies.
Optimally, the same physician should interpret the bone marrow aspirate smears and the core biopsy specimens, or the interpretations of those specimens should be correlated if performed by different physicians.
In addition to morphologic assessment (blood and bone marrow), the pathologist or treating clinician should obtain sufficient samples and perform conventional cytogenetic analysis (i.e., karyotype), appropriate molecular genetic and/or fluorescent in situ hybridization (FISH) testing, and flow cytometric immunophenotyping (FCI). The flow cytometry panel should be sufficient to distinguish acute myeloid leukemia (including acute promyelocytic leukemia), T-cell acute lymphoblastic leukemia (T-ALL) (including early T-cell precursor leukemias), B-cell precursor ALL (B-ALL), and acute leukemia of ambiguous lineage on all patients diagnosed with acute leukemia. Molecular genetic and/or FISH testing does not, however, replace conventional cytogenetic analysis (Strong recommendation).
Note: If sufficient bone marrow aspirate or peripheral blood material is not available for FCI, immunohistochemical studies may be used as an alternative method for performing limited immunophenotyping. In addition, a second bone marrow core biopsy can be obtained and submitted, unfixed in tissue culture media, for disaggregation for genetic studies and flow cytometry.
For patients with suspected or confirmed acute leukemia, the pathologist may request and evaluate cytochemical studies to assist in the diagnosis and classification of acute myeloid leukemia (AML) (Expert consensus opinion).
The treating clinician or pathologist may use cryopreserved cells or nucleic acid, formalin fixed, nondecalcified paraffin-embedded (FFPE) tissue, or unstained marrow aspirate or peripheral blood smears obtained and prepared from peripheral blood, bone marrow aspirate or other involved tissues for molecular or genetic studies in which the use of such material has been validated. Such specimens must be properly identified and stored under appropriate conditions in a laboratory that is in compliance with regulatory and/or accreditation requirements (Recommendation).
For patients with acute lymphoblastic leukemia (ALL) receiving intrathecal therapy, the treating clinician should obtain a cerebrospinal fluid (CSF) sample. The treating clinician or pathologist should ensure that a cell count is performed and that examination/enumeration of blasts on a cytocentrifuge preparation is performed and is reviewed by the pathologist (Strong recommendation).
For patients with acute leukemia other than those with ALL who are receiving intrathecal therapy, the treating clinician may, under certain circumstances, obtain a CSF sample when there is no clinical contraindication. The treating clinician or pathologist should ensure that a cell count is performed and that examination/enumeration of blasts on a cytocentrifuge preparation is performed and is reviewed by the pathologist (Expert consensus opinion).
For patients with suspected or confirmed acute leukemia, the pathologist may use flow cytometry in the evaluation of CSF (Recommendation).
For patients who present with extramedullary disease without bone marrow or blood involvement, the pathologist should evaluate a tissue biopsy and process it for morphologic, immunophenotypic, cytogenetic, and molecular genetic studies, as recommended for the bone marrow (Strong recommendation).
Note: Additional biopsies may be indicated to obtain fresh material for ancillary testing.

For patients with suspected or confirmed acute leukemia, the pathologist or treating clinician should ensure that flow cytometry analysis or molecular characterization is comprehensive enough to allow subsequent detection of minimal residual disease (MRD) (Strong recommendation).

For pediatric patients with suspected or confirmed B-ALL, the pathologist or treating clinician should ensure that testing for t(12;21)(p13.2;q22.1); *ETV6-RUNX1*, t(9;22)(q34.1;q11.2); *BCR-ABL1*, *KMT2A (MLL)* translocation, iAMP21, and trisomy 4 and 10 is performed (Strong recommendation).

For adult patients with suspected or confirmed B-ALL, the pathologist or treating clinician should ensure that testing for t(9;22)(q34.1;q11.2); *BCR-ABL1* is performed. In addition, testing for *KMT2A (MLL)* translocations may be performed (Strong recommendation for testing for t(9;22)(q34.1;q11.2) and *BCR-ABL1*; Recommendation for testing for *KMT2A (MLL)* translocations).

For patients with suspected or confirmed ALL, the pathologist or treating clinician may order appropriate mutational analysis for selected genes that influence diagnosis, prognosis, and/or therapeutic management, which includes, but is not limited to, *PAX5*, *JAK1*, *JAK2*, and/or *IKZF1* for B-ALL and *NOTCH1* and/or *FBXW7* for T-ALL. Testing for overexpression of CRLF2 may also be performed for B-ALL (Recommendation).

For pediatric and adult patients with suspected or confirmed AML of any type, the pathologist or treating clinician should ensure that testing for *FLT3-ITD* is performed. The pathologist or treating clinician may order mutational analysis that includes, but is not limited to, *IDH1*, *IDH2*, *TET2*, *WT1*, *DNMT3A*, and/or *TP53* for prognostic and/or therapeutic purposes (Strong recommendation for testing for *FLT3-ITD*; Recommendation for testing for other mutational analysis).

For adult patients with confirmed core-binding factor (CBF) AML (AML with t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* or inv(16)(p13.1q22) /t(16;16)(p13.1;q22); *CBFB-MYH11*), the pathologist or treating clinician should ensure that appropriate mutational analysis for *KIT* is performed. For pediatric patients with confirmed CBF-AML; *RUNX1-RUNX1T1* or inv(16)(p13.1q22) /t(16;16)(p13.1;q22); *CBFB-MYH11*—the pathologist or treating clinician may ensure that appropriate mutational analysis for *KIT* is performed (Strong recommendation for testing for *KIT* mutation in adult patients with CBF-AML; Expert consensus opinion for testing for *KIT* mutation in pediatric patients with CBF-AML).

For patients with suspected acute promyelocytic leukemia (APL), the pathologist or treating physician should also ensure that rapid detection of *PML-RARA* is performed. The treating physician should also order appropriate coagulation studies to evaluate for disseminated intravascular coagulation (DIC) (Strong recommendation).

For patients other than those with confirmed core binding factor AML, APL, or AML with myelodysplasia-related cytogenetic abnormalities, the pathologist or treating clinician should also ensure that mutational analysis for *NPM1*, *CEBPA*, and *RUNX1* is also performed (Strong recommendation).

For patients with confirmed acute leukemia, no recommendation is made for or against the use of global/gene-specific methylation, microRNA (miRNA) expression, or gene expression analysis for diagnosis or prognosis (No recommendation).

For patients with confirmed mixed phenotype acute leukemia (MPAL), the pathologist or treating clinician should ensure that testing for t(9;22)(q34.1;q11.2); *BCR-ABL1*, and *KMT2A (MLL)* translocations is performed (Strong recommendation).

All laboratory testing performed for the initial workup and diagnosis of a patient with acute leukemia must be performed in a laboratory that is in compliance with regulatory and/or accreditation requirements (Strong recommendation).

If after examination of a peripheral blood smear, it is determined that the patient will require immediate referral to another institution with expertise in the management of acute leukemia for treatment, the initial institution should, whenever possible, defer invasive procedures, including bone marrow aspiration and biopsies, to the treatment center to avoid duplicate procedures, associated patient discomfort, and additional costs (Strong recommendation).

If a patient is referred to another institution for treatment, the primary institution should provide the treatment center with all laboratory results, pathology slides, flow cytometry data, cytogenetic information, and a list of pending tests at the time of the referral. Pending test results should be forwarded when they become available (Strong recommendation).

In the initial report, the pathologist should include laboratory, morphologic, immunophenotypic, and, if performed, cytochemical data, on which the diagnosis is based, along with a list of any pending tests. The pathologist should issue addenda/amended reports when the results of additional tests become available (Strong recommendation).

The pathologist and treating clinician should coordinate and ensure that all tests performed for classification, management, predicting prognosis, and disease monitoring are entered into the patient's medical records (Strong recommendation).

Note: This information should include the sample source, adequacy, and collection information, as applicable.

Treating physicians and pathologists should use the current World Health Organization (WHO) terminology for the final diagnosis and classification of acute leukemia (Strong recommendation).

Definitions

Grades for Strength of Evidence*

Designation	Description	Quality of Evidence
Convincing	High confidence that available evidence reflects true effect. Further research is very unlikely to change the confidence in the estimate of effect.	High-quality to intermediate-quality evidence
Adequate	Moderate confidence that available evidence reflects true effect. Further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate.	Intermediate-quality to low-quality of evidence
Inadequate	Little confidence that available evidence reflects true effect. Further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate.	Low or insufficient evidence, and expert panel used formal consensus process to reach recommendation
Insufficient	Evidence is insufficient to discern net effect. Any estimate of effect is very uncertain.	Insufficient evidence, and expert panel used formal consensus process to reach recommendation

*Adapted from Balshem H, Helfand M, Schunemann HJ, et al.430 GRADE guidelines, 3: rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401–406; copyright 2011, with permission from Elsevier.

Grades for Strength of Recommendations*

Designation	Recommendation	Rationale
Strong Recommendation	Recommend for, or against, a particular practice. (Can include "must" or "should.")	Supported by convincing (high) or adequate (intermediate) quality of evidence and clear benefit that outweighs any harms.
Recommendation	Recommend for, or against, a particular practice. (Can include "should" or "may.")	Some limitations in quality of evidence (adequate [intermediate] or inadequate [low]), balance of benefits and harms, values, or costs, but panel concluded that there is sufficient evidence and/or benefit to inform a recommendation.
Expert Consensus Opinion	Recommend for, or against, a particular practice. (Can include "should" or "may.")	Serious limitations in quality of evidence (inadequate [low] or insufficient), balance of benefits and harms, values, or costs, but panel consensus was that a statement is necessary.
No Recommendation	No recommendation for, or against, a particular practice	Insufficient evidence or agreement of the balance of benefits and harms, values, or costs to provide a recommendation.

*Derived from Andrews J, Guyatt G, Oxman AD, et al. GRADE Guidelines, 14: going from evidence to recommendations: the significant and presentation of recommendations. J Clin Epidemiol. 2013;66(7):719-725.

Clinical Algorithm(s)

The following algorithms are provided in the *Initial Diagnostic Workup of Acute Leukemia. A Pocket Guide for the Clinician* (see the "Availability of Companion Documents" field):

Initial diagnostic workup of acute leukemia
Initial diagnostic workup of lymphoblastic leukemia
Initial diagnostic workup of acute myeloid leukemia

Scope

Disease/Condition(s)

Acute leukemia

Guideline Category

Diagnosis

Evaluation

Clinical Specialty

Hematology

Oncology

Pathology

Intended Users

Clinical Laboratory Personnel

Physician Assistants

Physicians

Guideline Objective(s)

- To recommend laboratory testing for the initial workup for proper diagnosis, determination of prognostic factors, and possible future monitoring of acute leukemias (ALs), including acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL) and ALs of ambiguous lineage, in children and adults
- To answer the following key questions:
  - What clinical and laboratory information should be available during the initial diagnostic evaluation of a patient with AL?
  - What specimens and sample types should be evaluated during the initial workup of a patient with AL?
  - At the time of diagnosis, what tests are required for all patients for the initial evaluation of an AL?
  - Which tests should be performed on only a subset of patients, including in response to results from initial tests and morphology?

- Where should laboratory testing be performed?
- How should test results and the diagnosis be correlated and reported?

Target Population

Patients suspected of having acute leukemia (AL)

Interventions and Practices Considered

1. Comprehensive sharing and reporting of clinical data and physical exam and imaging findings
2. Collection and evaluation of samples/specimens
    - Complete blood count (CBC)
    - Leukocyte differentials
    - Peripheral blood smear
    - Morphological evaluation and ancillary studies
    - Conventional cytogenetic analysis (i.e., karyotype)
    - Molecular genetic testing
    - Fluorescent in-situ hybridization (FISH) testing
    - Flow cytometric immunophenotyping (FCI)
    - Immunohistochemical stains
    - Cytochemical studies
    - Choice of cell type for testing
    - Cerebrospinal fluid (CSF) sample
    - Flow cytometry analysis
    - Molecular characterization
    - Genetic testing and mutational analysis
3. Deferral of invasive procedures after referral to another institution
4. World Health Organization (WHO) classification scheme for reporting acute leukemia (AL)

Major Outcomes Considered

- Survival rates (e.g., overall survival [OS], disease free survival [DFS])
- Utility and technical requirements of bone marrow aspirate for diagnosis of acute leukemia (AL)
- Utility and technical requirement of core biopsy for diagnosis of AL
- Utility of bone marrow clot section for the diagnosis of AL
- Utility of bone marrow touch preparation for the diagnosis of AL
- Utility of antigens for the diagnosis of acute myeloid leukemia (AML), acute promyelocytic leukemia (APL), and acute lymphocytic leukemia (ALL)
- Utility of minimal residual disease (MRD) in AML, ALL, and mixed phenotype acute leukemia (MPAL)
- Significant differences in blood versus marrow for flow cytometry in diagnosis of AL
- Significant differences in blood versus marrow for MRD
- Utility of antigens in detection of MRD in AML, ALL, and MPAL
- Differences in MRD by flow cytometry versus MRD by molecular studies/sequences
- Utility of engraftment studies for detection of MRD after transplant for AL
- Antigens detected by flow cytometry for therapeutic target in AML, ALL, and MPAL
- Survival rates by test type
- Differences in diagnosis or in test results when duplicate tests were performed in more than one institution
- Classification scheme for reporting AL

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Literature Search and Selection

A systematic literature search was completed on October 4, 2011, for relevant evidence using OvidSP (Ovid Technologies, New York, New York), PubMed (U.S. National Library of Medicine, Bethesda, Maryland), and Science Direct (Elsevier, Amsterdam, the Netherlands) to identify literature published from January 2005 through September 2011. A literature refresh was completed on April 24, 2013, and again on August 11, 2015, to identify recently published material. Database searches were supplemented with expert panel recommendations and the references from those supplemental articles were reviewed to ensure all relevant publications were included.

Selection at all 3 levels of the systematic review (SR) was based on predetermined inclusion/exclusion criteria for the outcomes of interest. Detailed information about the literature search and selection can be found in the supplemental digital content (SDC) (see the "Availability of Companion Documents" field).

Number of Source Documents

Of the 4901 unique studies identified in the systematic review (SR), 174 published, peer-reviewed articles were included, which underwent data extraction and qualitative analysis. Among the extracted documents, 55 articles/documents did not meet any inclusion criteria and were excluded from the SR but retained for discussion purposes.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Grades for Strength of Evidence*

Designation	Description	Quality of Evidence
Convincing	High confidence that available evidence reflects true effect. Further research is very unlikely to change the confidence in the estimate of effect.	High quality to intermediate-quality evidence
Adequate	Moderate confidence that available evidence reflects true effect. Further research is likely to have an important effect on the confidence in the estimate of effect and may change the estimate.	Intermediate-quality to low-quality of evidence
Inadequate	Little confidence that available evidence reflects true effect. Further research is very likely to have an important effect on the confidence in the estimate of effect and is likely to change the estimate.	Low or insufficient evidence, and expert panel used formal consensus process to reach recommendation
Insufficient	Evidence is insufficient to discern net effect. Any estimate of effect is very uncertain.	Insufficient evidence, and expert panel used formal

Designation	Description	Quality of Evidence
		consensus process to reach recommendation

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Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Data Extraction and Management

The data elements from an included article/document were extracted by one reviewer into standard data formats and tables developed using the systematic review database software, DistillerSR (Evidence Partners Inc., Ottawa, Canada); a second reviewer confirmed accuracy and completeness. Any discrepancies in data extraction were resolved by discussion between the co-chairs and the methodologist. A bibliographic database was established in EndNote (Thomson Reuters, Carlsbad, CA) to track all literature identified and reviewed during the study.

Quality Assessment

An assessment of the quality of the evidence was performed for all retained studies after application of the inclusion and exclusion criteria by the methodologist (see Table 6 in the supplemental digital content [SDC] [see the "Availability of Companion Documents" field]). Using that method, studies deemed to be of low quality would not be excluded from the systematic review (SR) but would be retained and their methodological strengths and weaknesses discussed where relevant. Studies would be assessed by confirming the presence of items related to both internal and external validity, which are all associated with methodological rigor and a decrease in the risk of bias. The quality assessment of the studies was performed by determining the risk of bias by assessing key indicators based on study design against known criteria. Only studies obtained from the panel's SR were assessed for quality by these methods and any additional articles brought in to support the background and to contextualize the findings were not. Each study was assessed individually (refer to the SDC for individual assessments and results by guideline statement) and then summarized by study type. A summary of the overall quality of the evidence was given considering the evidence in totality.

A rating for the strength of evidence is given for guideline statements for which quality was assessed (i.e., only studies obtained from the panel's SR). Ultimately, the designation (rating) of the strength of evidence is a judgment by the expert panel of their level of confidence that the evidence from the studies informing the recommendations reflects a true effect. See the "Rating Scheme for the Strength of the Evidence" field for a description of the grades for strength of evidence. Refer to the SDC for a detailed discussion of the quality assessment.

Methods Used to Formulate the Recommendations

Expert Consensus (Nominal Group Technique)

Description of Methods Used to Formulate the Recommendations

Panel Composition

The College of American Pathologists (CAP) Pathology and Laboratory Quality Center (the Center) and the

American Society of Hematology (ASH) members included 7 pathologists, one hematologist, one hematologist/oncologist, and one methodologist consultant. These panel members served as the expert panel (EP) for the systematic evidence review and development of the guideline statements. An advisory panel including one patient advocate, one cytogeneticist, 3 hematologists/oncologists (including one pediatric hematologist/oncologist), one medical oncologist, and 2 hematopathologists assisted the EP in determining the project scope and reviewing and providing guidance on the draft recommendations and manuscript development.

Assessing the Strength of Recommendations

Development of recommendations required that the EP review the identified evidence and make a series of key judgments, including the balance of benefits and harms. Grades for strength of recommendations were developed by the CAP Pathology and Laboratory Quality Center and are described in the "Rating Scheme for the Strength of the Recommendations" field.

Results

The expert panel (EP) met 23 times through teleconference webinars from June 8, 2011, through August 16, 2016. Additional work was completed via email. The panel met in person July 19, 2013, to review evidence to date and draft recommendations.

A public comment period was held from August 10 through August 31, 2015, on the ASH Web site. Twenty-nine draft recommendations and 2 demographic questions were posted for peer review.

Agree and *disagree* responses were captured for every proposed recommendation. The Web site also received 789 written comments. Twenty-six draft recommendations achieved more than 90% agreement, 2 draft statements achieved more than 80% to 90% agreement, and 1 received more than 70% to 80% agreement. Each EP member was assigned 3 draft statements for which they had to review the public comments and present them to the entire panel for group discussion. After consideration of the comments, 2 draft recommendations were maintained with the original language, 25 were revised, and 2 draft recommendations were combined into other statements, which resulted in 27 final recommendations.

The panel convened again on September 14, 2015, to review the comments received and revise the recommendations. Resolution of all changes was obtained by unanimous consensus of the panel members using a nominal group technique (rounds of subsequent teleconference webinars and email discussions). Final EP recommendations were approved by a formal vote. The panel considered laboratory efficiency and feasibility throughout the entire process, although neither cost nor cost-effectiveness analyses were performed.

Refer to the original guideline document for public comment response to each guideline statement.

Rating Scheme for the Strength of the Recommendations

Grades for Strength of Recommendations*

Designation	Recommendation	Rationale
Strong Recommendation	Recommend for, or against, a particular practice. (Can include "must" or "should.")	Supported by convincing (high) or adequate (intermediate) quality of evidence and clear benefit that outweighs any harms.
Recommendation	Recommend for, or against, a particular practice. (Can include "should" or "may.")	Some limitations in quality of evidence (adequate [intermediate] or inadequate [low]), balance of benefits and harms, values, or costs, but panel concludes that there is sufficient evidence and/or benefit to inform a recommendation.

Designation	Recommendation	Rationale
Expert Consensus Opinion	Recommend for, or against, a particular practice. (Can include "should" or "may.")	Serious limitations in quality of evidence (inadequate [low] or insufficient), balance of benefits and harms, values, or costs, but panel consensus is that a statement is necessary.
No Recommendation	No recommendation for, or against, a particular practice	Insufficient evidence or agreement of the balance of benefits and harms, values, or costs to provide a recommendation.

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Cost Analysis

The panel considered laboratory efficiency and feasibility throughout the entire process, although neither cost nor cost-effectiveness analyses were performed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

A draft guideline was developed by the expert panel (EP) and was modified based on comments received during an open-comment period.

A public comment period was held from August 10 through August 31, 2015, on the American Society of Hematology (ASH) Web site. Twenty-nine draft recommendations and 2 demographic questions were posted for peer review.

An independent review panel, masked to the EP and vetted through the conflict of interest process, provided a review of the guideline and recommended the guideline for approval by the College of American Pathologists (CAP) Council on Scientific Affairs and the American Society of Hematology (ASH) Executive Committee.

Refer to the supplemental digital content (SDC) (see the "Availability of Companion Documents" field) for additional information.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- The evidence shows that providing relevant data from clinical, physical examination, and imaging findings, aid in the initial diagnosis of acute leukemia and a more accurate diagnosis.
- The panel believes that recommending a fresh bone marrow aspirate for all patients suspected of AL will decrease diagnostic errors.
- Including cytogenetic analysis, appropriate molecular genetic and/or fluorescent in-situ hybridization (FISH) testing and flow cytometric immunophenotyping will result in a more standardized initial workup which will likely reduce the need for repeat procedures/studies. Furthermore, these studies allow identification of parameters that may comprise a "fingerprint" of the leukemia and allow for detection of minimal residual disease in future specimens.
- Saving unused cells from the initial marrow procedure could circumvent an additional marrow procedure to obtain cells that might be necessary for additional diagnostic or prognostic studies, or to identify targets for therapy directed at specific antigens or genetic abnormalities.
- For patients with suspected or confirmed acute leukemia, the panel believes using flow cytometry in the evaluation of cerebrospinal fluid (CSF) will help resolve morphologically difficult cases.
- Obtaining a CSF sample for appropriate patients and ensuring that a cell count is performed and that examination/enumeration of blasts on a cytocentrifuge preparation is performed ensures that the pathologist has the specimens needed and the data from the specimen to inform an accurate diagnosis.
- The specific genetic tests and mutational analyses all aid in improved prognosis determination and/or provide the treating clinician with information needed to make treatment decisions such as specific targeted therapy. One of the biggest benefits is that by providing these recommendations, pathologists who workup acute leukemia will be aware of the specific tests required for certain subsets of patients.
- Deferring invasive procedures at the original institution after referral to another institution should result in better, coordinated care, increased comfort for the patient, and in cost savings.
- The benefits of providing the referred treatment center with all laboratory results, pathology slides, flow cytometry data, cytogenetic information, and a list of pending tests at the time of the referral are that treatment centers will have the information and laboratory assets necessary to properly treat patients including knowledge of tests ordered, but have information regarding which results are still pending. This should result in improved coordinated care and cost savings.
- The benefits of the pathologist including laboratory, morphologic, immunophenotypic, and, if performed, cytochemical data, on which the diagnosis is based, along with a list of any pending tests in the initial report are that the laboratory report will contain the results for each of the elements used to render a diagnosis and that this information will be visible to both laboratory personnel and treating clinicians.
- The pathologist and treating clinician coordinating and ensuring that all tests performed for classification, management, predicting prognosis and disease monitoring are entered into the patient's medical records should improve patient care by ensuring that the treating physicians have all available information with an appropriate and integrated interpretation.
- The major benefit of using the World Health Organization (WHO) schema is that physicians will have a consistent understanding of diagnosis and classification of AL regardless of geographic parameters.

Refer to the original guideline document and supplemental digital content (SDC) (see the "Availability of Companion Documents" field) for benefits of specific recommendations.

Potential Harms

- An undesirable effect of fresh bone marrow aspirate might be the risk of complications resulting from performing the bone marrow procedure, especially the core biopsy.
- Improper handling/storage of unused cells from the initial marrow procedure may result in false test results.
- The most common risks involved in obtaining a cerebrospinal fluid (CSF) sample are discomfort/pain, infection, and bleeding.
- If the clinical context of deferring invasive procedures is misinterpreted, it could result in delayed

care.

Refer to the original guideline document and supplemental digital content (SDC) (see the "Availability of Companion Documents" field) for harms of specific recommendations.

Contraindications

Contraindications

There may be contraindications to obtaining a cerebrospinal fluid (CSF) sample in some patients, particularly when the peripheral blast count is high.

Qualifying Statements

Qualifying Statements

Practice guidelines and consensus statements reflect the best available evidence and expert consensus supported in practice. They are intended to assist physicians and patients in clinical decision-making and to identify questions and settings for further research. With the rapid flow of scientific information, new evidence may emerge between the time a practice guideline or consensus statement is developed and when it is published or read. Guidelines and statements are not continually updated and may not reflect the most recent evidence. Guidelines and statements address only the topics specifically identified therein and are not applicable to other interventions, diseases, or stages of diseases. Furthermore, guidelines and statements cannot account for individual variation among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It is the responsibility of the treating physician or other health care provider, relying on independent experience and knowledge, to determine the best course of treatment for the patient. Accordingly, adherence to any practice guideline or consensus statement is voluntary, with the ultimate determination regarding its application to be made by the physician in light of each patient's individual circumstances and preferences. The College of American Pathologists (CAP) and American Society of Hematology (ASH) make no warranty, express or implied, regarding guidelines and statements and specifically excludes any warranties of merchantability and fitness for a particular use or purpose. The CAP and ASH assume no responsibility for any injury or damage to persons or property arising out of, or related to any, use of this statement or for any errors or omissions.

Implementation of the Guideline

Description of Implementation Strategy

Dissemination Plans

The College of American Pathologists (CAP) plans to host an Initial Diagnostic Workup of Acute Leukemia resource page which will include a link to the manuscript and supplement; a summary of the recommendations, a teaching PowerPoint (Microsoft Corporation, Redmond, WA), a frequently asked question (FAQ) document, and an infographic. The guideline will be promoted and presented at various society meetings.

Implementation Tools

Pocket Guide/Reference Cards

Quick Reference Guides/Physician Guides

Resources

Slide Presentation

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Arber DA, Borowitz MJ, Cessna M, Etzell J, Foucar K, Hasserjian RP, Rizzo JD, Theil K, Wang SA, Smith AT, Rumble RB, Thomas NE, Vardiman JW. Initial diagnostic workup of acute leukemia: guideline from the College of American Pathologists and the American Society of Hematology. Arch Pathol Lab Med. 2017 Oct;141(10):1342-93. [431 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2017 Oct

Guideline Developer(s)

American Society of Hematology - Medical Specialty Society

College of American Pathologists - Medical Specialty Society

Source(s) of Funding

The College of American Pathologists (CAP) and American Society of Hematology (ASH) provided funding for the administration of the project; no industry funds were used in the development of the guideline. All panel members volunteered their time and were not compensated for their involvement, except for the contracted methodologist.

Guideline Committee

The College of American Pathologists (CAP) Pathology and Laboratory Quality Center and the American Society of Hematology (ASH) Expert Panel

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

Conflict of Interest Policy

In accordance with the College of American Pathologists (CAP) conflict of interest policy (in effect April 2010), members of the expert panel disclosed all financial interests of possible relevance to the guideline, from 12 months before appointment through publication of the guideline. Individuals were instructed to disclose any relationship that could be interpreted as constituting an actual, potential, or apparent conflict. Disclosures were collected by the CAP staff before beginning the systematic review (SR) and were updated continuously throughout the project at each virtual and face-to-face meeting. A separate oversight group (consisting of staff and members of the CAP and American Society of Hematology [ASH]) reviewed the disclosures and agreed that most of the expert panel had no conflicts of interest. Complete disclosures of the expert panel members are listed in the Appendix of the original guideline document. Disclosures of interest judged by the oversight group to be conflicts are as follows: D.A.A., consultancy and board/advisory board with Celgene Corporation (Summit, New Jersey), board/advisory board of DAVA Oncology (Dallas, Texas), Bristol-Myers Squibb (New York, New York), Novartis (Deerfield, Illinois), and Agios Pharmaceuticals (Cambridge, Massachusetts); M.J.B., grants received from Amgen Inc (Thousand Oaks, California), Beckman Coulter (Brea, California), Becton, Dickinson and Company (San Jose, California), Bristol- Myers Squibb (New York, New York), Genzyme Corporation (Cambridge, Massachusetts), MedImmune (Gaithersburg, Maryland), and Micromet (Rockville, Maryland); K.F., consultancy with Celgene Corporation (Summit, New Jersey); R.P.H., consultancies with Cancer and Leukemia Group B, Genzyme Corporation (Cambridge, Massachusetts), and Incyte Corporation (Wilmington, Delaware); S.A.W., consultancy with Genzyme Corporation (Cambridge, Massachusetts), board/advisory board with, and grants received from, Seattle Genetics, Inc (Bothell, Washington), and GlaxoSmithKline plc (Brentford, United Kingdom). Most of the EP (6 of 11 members) was assessed as having no relevant conflicts of interest. See the supplemental digital content (see the "Availability of

Companion Documents" field) for full details on the conflict of interest policy.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Archives of Pathology & Laboratory Medicine Journal Web site .

Availability of Companion Documents

The following are available:

- Initial diagnostic workup of acute leukemia. Supplemental digital content. Northfield (IL): College of American Pathologists (CAP); 2017 Feb. 69 p. Available from the College of American Pathologists (CAP) Web site .
- Initial diagnostic workup of acute leukemia guideline. Summary of recommendations. Northfield (IL): College of American Pathologists (CAP); 2017. 4 p. Available from the CAP Web site .
- Initial diagnostic workup of acute leukemia. Frequently asked questions. Northfield (IL): College of American Pathologists (CAP); 2017 Feb 22. 3 p. Available from the CAP Web site .
- Initial diagnostic workup of acute leukemia. Teaching presentation. Northfield (IL): College of American Pathologists (CAP); 2017 Feb 22. 52 p. Available from the CAP Web site .
- Initial diagnostic workup of acute leukemia. Infographic. Northfield (IL): College of American Pathologists (CAP); 2017. 1 p. Available from the CAP Web site .
- Initial diagnostic workup of acute leukemia. A pocket guide for the clinician. Northfield (IL): College of American Pathologists (CAP); 2017 Mar. 4 p. Available from the CAP Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on January 24, 2018. The information was verified by the guideline developer on February 13, 2018.

This NEATS assessment was completed by ECRI Institute on December 14, 2017. The information was verified by the guideline developer on February 13, 2018.

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